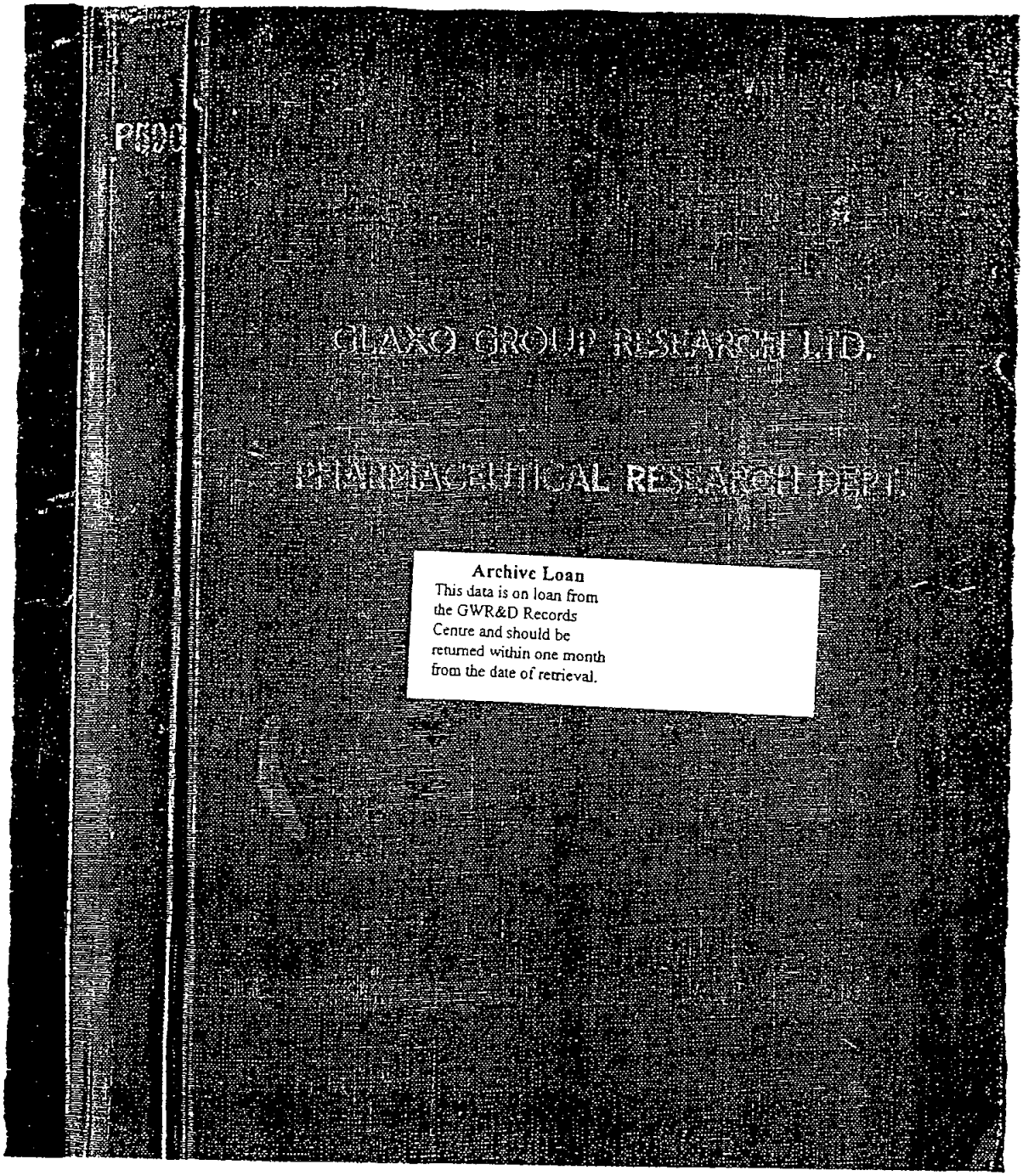
8



PLAINTIFF'S TRIAL EXHIBIT 238

11

Samples removed from stability program PR2607 - after storage at 37°/50%RH for 16-17 months. This is considered approx. equivalent to 2 years at 30°. Symp batch no: B55/84.

NTH - 300mL Approx full volume = 303mL

add 15.15 g absolute alcohol to give a 5% v/v addition of Absolute Alcohol AR (99.7%) B/N PS54/33 ethanol

Inoculum - 10^6/ml Ps cepacia. Stand date - 6/3/85.

[for this exp 2 x 200ml bottles, 8.7/85 used. 15/8/85.
10.1 g ETOH for 5% v/v in 200mL bottle of symp. B.No Alcohol - PS54/33]

RESULTS.

	Inoc/ml	0hr	6hr	D2	D7	D21
NTH (PR2607).	1.9×10^6	3×10^3		<10	<10	<10 <10.

This formulation is successful against challenge with Ps cepacia 10^6/ml

9/9/85

A sample was obtained from B-lab for ARD to examine for hydroxybenzoate and ethanol concentrations. J Wilson. see page 33.

Stability of Ranitidine in the presence of 5% v/v alcohol.

so far

ARD have shown that 5% alcohol in the formulation does not affect the stability of ranitidine.

An investigation into the stability of the hydroxybenzoates in the presence of alcohol will be made. see page 31. and PS2. J Wilson 11/9/85.

118

5.0% w/v, 3.0% w/v and 1.0% w/v Ethanol in Zantac Syrup containing Propyl hydroxybenzoate and Butyl hydroxybenzoate at 70% of their target conc.

Introduction

It has already been demonstrated that 5% w/v EtOH in Zantac syrup (Prelim. formulation containing methyl paraben) inhibits proliferation of Ps. capacia P590/11. After 5 hrs no bugs are detected. The alcohol in some way potentiates the action of the hydroxybenzoates. The formulation without methyl must be tested in this way. A 300ml bottle of the syrup containing 5% EtOH as well as reduced levels of alcohol will also be examined by B-lab.

RESULTS.

5% w/v EtOH	Inoc	0hr	6hrs	2 days	7 days.
rec'd 21/8/85.	5.9×10^6	5.2×10^4	6.7×10^4	6.0×10^3.	4×10^1
				14 21 28	
				<10 <10 <10	

9/9/85 * This formulation is effective against Ps. capacia.

Sample supplied to BRD for analysis of preservative and ethanol concentrations. see page 33. J Wilson.

3% w/v EtOH	"	9.4×10^4	8.3×10^4	6.4×10^4	1.5×10^5.
rec'd 21/8/85.		D14 3.5×10^5	D21 1.6×10^5	D28 4.5×10^5.	

Conclusion - Ineffective against the organism Ps capacia. Not proceeded any further.

1% w/v EtOH	"	0hr	6hrs	2 days	7 days
rec'd 22/8/85.		5.1×10^4	6.4×10^4	4.9×10^5.	5.4×10^5
		14 Days	21 Days	28 Days	
		2.9×10^5	2.5×10^5	2.0×10^5.	

Conclusion - Ineffective against Ps. capacia. Not proceeded any further.

5.3

(FORMULA = ORIGIN)

RANITIDINE SYRUP CONTAINING 7.5%w/v ETHANOL

The formulation proposed for marketing is to be progressed further. Meeting on 7/10/85 decided that 7.5%w/v EtOH should be included in the formulation. This should ensure that a minimum of 5.0%w/v will remain at the end of life of the product.

To examine the method of manufacture and determine whether 7.5%w/v EtOH has no detrimental effects on the stability of the HPMC etc a small scale batch is to be prepared prior to manufacture of stability batches of 100L or so.

Formula	%w/v	1.0L	B/No.
Ranitidine HCl	1.68	16.8g ✓	3755-8783
Propyl Hydroxybenzoate B.P.	0.015	0.15g ✓	NA0297
Butyl Hydroxybenzoate B.P.	0.0075	0.075g ✓	M14878
Absolute Alcohol B.P.	7.5	75.0g ✓	P5543
HPMC 2910 USP Visc Type 4,000 cp	0.45	4.5g ✓	QP8204160SE
KH_2PO_4	N.F 0.095	0.95g ✓	9281420D
Na_2HPO_4	U.S.P. 0.35	3.5g ✓	9236000D
NaCl	B.P. 0.10	1.0g ✓	SK8845
Sacch Na.	B.P. 0.03	0.3g ✓	W85147
Sorbitol Solution B.P.C.	10.0	100.0g ✓	E154E
Mint Flavour IFF 17.42.3632	0.5	5.0g ✓	12261
~~Purified~~ Distilled Water to	100mL	1.0L ✓	—

The pH of the syrup was measured as:-

LAST PRODUCT 25852 9-10 CLEANED

CLEANED BY A.S.

293

5/6/86

Arrhenius Equation Calculations in the Stability of Zantac Syrup.

Introduction

Numerous ranitidine syrup stability programmes are under way but at present only limit data are available. Hence to predict the shelf-life resume must be made to the Arrhenius equation.

Programmes

Details of the programmes analysed are as follow.

PR No.	Formula	Batch no.	Container	Ethanol?	Time point
2713	UK	B332/84	300ml Glass	No	12 months
2714	UK	B332/84	200ml Glass	No	12 "
2828	UK	B272/85	300ml Glass	Yes	6 "
2829	UK	B273/85	300ml Glass	Yes	6 "
2739	USA	B12/85	16oz Glass	No	12 "
2738	USA	B514/85	16oz Glass	No	12 "
2833	USA	B289/85	16oz PET	Yes	6 "
2835	USA	B270/85	16oz PET	Yes	6 "
2839	USA	B291/85	16oz PET	Yes	6 "
2729	USA	B13/85	16oz PET	No	12 "
2730	USA	B15/85	16oz PET	No	12 "
2834	USA	B289/85	16oz Glass	Yes	3 "
2836	USA	B290/85	16oz Glass	Yes	7 "
2840	USA	B291/85	16oz Glass	Yes	3 "

Calculations - 1

① At each time point the 4°C assay value is taken as 100% and the ranitidine content expressed as a percentage of this. (mean assay value)

② The t½ values (time for 5% loss of ranitidine to occur) at each temperature are calculated from a plot of ln(% ranitidine) vs time (months). The 4 week time point is taken at 0.9 months. The data are force fitted through the time origin at a ranitidine content of 100%. The best fit line is calculated and used to give the time for t5% at each temperature.

③ The data from ② when the plotted as ln(t5%) vs T^{-1} (where T is absolute temperature) and used to predict the t5% values at 20, 25, 30, 37 and 45°C from the best fit line. Data @ 20°C from ② was not used due to high variability.

Results

Programme Number

AR 2713	2713	2714	2823	2829	2738	2739	2833	2835	2831
Temp °C	Time								
20	3								
20	6								
20	12								
30	3								
30	6								
30	12								
37	3								
37	6								
37	12								
45	3								
45	6								
45	12								

P.T.O